REMARKS

Rejections under 35 USC § 112:

Claims 1 and 3-17 have been rejected under 35 USC 112 first paragraph for failing to describe the nucleic acid modifying agent in such a way that one skilled in the art could distinguish nucleic acid modifying agents that could be used in the claimed method from nucleic acid modifying agents that could not be used in the method claimed. Applicants have amended the claims to describe the modification of the nucleic acid and obviate the rejection. Specifically, claim 1 has been modified to cite attachment of a compound to the nucleic acid at the N7 position of a guanine. Support for the amendment can be found in the specification on page 15 lines 3-11.

Claims 1 and 3-17 have been rejected under 35 USC 112 for not reasonably providing enablement for a process for nucleic acid delivery to a cell *in vivo*. The office action states on page 7 that the specification does not provide an enabled use for the method. The office action further states that the only intended use for the claimed method is gene therapy and that gene therapy is not enabled. Also, on page 8, the office action states "delivering a nucleic acid to a cell is not in and of itself a patentable utility." Applicants respectfully disagree. It is the Applicants' opinion that while therapeutic effects may be a derivative of gene therapy, the definition of the terminology "gene therapy" is not limited to that single result. The National Cancer Institute defines gene therapy as "treatment that alters a gene (the basic units of heredity found in all cells in the body)." On page 5 lines 6-21 of the specification, Applicants have defined the terms "therapeutic" and "therapeutic results" as "levels of gene products, including reporter (marker) gene products, which indicate a reasonable expectation of gene expression using similar compounds (nucleic acids), at levels considered sufficient by a person having ordinary skill in the art of gene therapy." This definition does not limit gene therapy to providing a therapeutic result. Applicants assert that in addition to obtaining therapeutic effects, other aspects are encompassed by the term. Among them are gene delivery methods and delivery of genes for research purposes. Delivery of modified nucleic acid allows improved delivery of the nucleic acid and tracking of a nucleic acid *in vitro* or *in vivo*. Tracking of a labeled (modified) gene is very useful in studying and developing other gene delivery methods.

Applicants have commercially developed and sold nucleic acid modification agents for research and development. These agents have been used by researchers in tracking nucleic

acid in cells. Rebuffat et al. Nature Biotech. 2001 used DNA modified by attachment of a fluorescent label to track delivery of the DNA to cells *in vitro* (see Fig. 5 on page 1158). Arima et al. Bioconjugate Chem. 2001 and Kihara et al. Bioconjugate Chem. 2002 examined methods to "improve the transfection efficiency of nonviral vector." In their studies, they used fluorescently modified DNA to follow the fate and intracellular location of the DNA (see Fig. 8 on page 483 of Arima et al. and Fig. 9 on page 1218 of Kiharu et al.). Salman et al. PNAS 2001 used modified DNA to study the kinetics and mechanism of DNA uptake in the cell nucleus. Klugherz et al. Nature Biotech. 2000, used modified DNA to monitor adherence of DNA to a stent. The labeled DNA could have been further used to track transfer of the DNA from the stent to vessel cells *in vivo*. Historically, researchers have used radioactively labeled DNA to study the distribution of delivered DNA *in vitro* and *in vivo*. The Applicants' invention provides for attachment of other, nonradioactive, labels and compounds to nucleic acid.

The Action states that "delivering a nucleic acid to a cell is not in and of itself a patentable utility." Applicants respectfully disagree and point out that an vast body of research is focused solely on methods to delivery nucleic acid to cells. Nevertheless, the Applicants have not claimed the mere delivery of a nucleic acid to a cell, but the delivery of an expressible nucleic acid to a cell, " The present invention relates to a process of modifying a gene (either within or outside an expressible sequence) such that the gene can be efficiently expressed in a cell" (page 14, lines 24-26). The modification is used for: "marking of the gene sequence for identification within cells, to augment it's delivery into the cell over that of unmodified sequences, or to facilitate increased expression of the gene product."

On page 12 lines 18-27, of the specification, "The use of modified DNA utilizing modifying chemical attachment bonding chemistry to generate an augmented immune response against an expressed polypeptide" is disclosed. Example 6 on page 26 demonstrates an enhanced *in vivo* immune response to a protein expressed from a modified nucleic acid, thus providing *in vivo* utility. Induction of immune response can have both therapeutic and non-therapeutic applications. An example of a non-therapeutic use is the production of antibodies (such as in mice) for research purposes. An example of a therapeutic use is genetic vaccination.

Example 5 on pages 24-26 demonstrates improved *in vivo* delivery when plasmid DNA is modified by attachment of a targeting peptide, in this case a nuclear localization signal.

Example 8 on page 31-43 demonstrates improved *in vivo* delivery of plasmid DNA modified by attachment of the *Label*IT®Trimer nucleic acid modifying agent.

By disclosing methods of using modified nucleic acid in: tracking of a nucleic acid, improving delivery of nucleic acid and enhancing an immune response, Applicants believe they have taught "how delivering a nucleic acid to a cell is to be applied to a real world problem." Applicants further believe that other applications will be readily recognized by those practicing the art or delivery nucleic acids to cells.

Claims 1-17 have been rejected as being indefinite with respect to the recitation of the term "nucleic acid modifying agent." Applicants have amended the claim 1 to remove the term.

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 1, 3-5 and 7-16 should be allowable.

Respectfully submitted,

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I hereby certify that this correspondence is being sent by United States Postal Service Express Mail to: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450 on this date: Dec. 22. 2003 .

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